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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/834,792	04/13/2001	Robert F. Margolskee	34116/1051	8395

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EXAMINER	
TURNER, SHARON L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/834,792	MARGOLSKEE ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17 and 24-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17 and 24-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4-14-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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Response to Amendment

1. The amendment filed 4-7-05 has been entered into the record and has been fully considered.

2. Estacion et al., and Okada et al., are removed as prior art in view of the amendment to the claims directing the structural limitation of SEQ ID NO:4.

3. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

4. Review of the prosecution history is now pertinent. The 112 2nd paragraph rejection previously of record (10-1-03) was withdrawn in view of Applicant's arguments that the skilled artisan would know suitable assays for assessing activation and inhibition of TRP8 as established in the prior art. This argument was persuasive as evidenced by the prior art newly cited in the Office Action of 10-4-04 as necessitated by amendment (the claims are newly drawn to TRP8 of SEQ ID NO:4, see Zucker et al., 102(e) US 2002/0164645). Zucker establishes suitable measurements for TRP8 activation and inhibition of taste receptor cell responses including for salty, sour, bitter and sweet sensations as well as methods for assessing compounds that modulate, activate and inhibit such taste signaling responses. Applicant's were placed on notice that obviation of the new matter rejection may remove Zucker from the available prior art of record, and thereby remove the basis for withdrawal of the 112, second paragraph rejection of record. In that case, the rejection may be reinstated absent further evidence within the piror art that establishes well known assays for the assessment of TRP8 activation and/or inhibtion and how such correlates to the perception of a bitter as

opposed to a sweet taste. While applicants have argued that such is within the skill of the art, no such evidence was presented in Applicant's response and the only such evidence/relevant reference found by the examiner is Zucker, now cited and relied upon for withdrawal of the rejection.

Instant amendment of 4-14-05 clarifies the invention in terms of the specification effective to receive the benefit of the noted priority date of 4-17-00 and removes Zucker as noted prior art. Applicants assert that guidance is provided to suitable assays as denoted within the specification, for assessing TRP8 activation as indicated via Hoffman, Liu and Parawitt with respect to TRPM5 (published in 2003) and for electrophysiological monitoring as in Gillo, Burnashev and Hu (published within 1994-1996). However, Hoffman Liu and Parawitt were not privy to the artisan and the time of invention in 2000, (i.e., the references were published in 2003). While Gillo, Burnashev and Hu evidence methods for assessing electrophysiological measurement including of calcium flux, the references are not on point to TRP8, do not clarify such measurements with respect to TRP8 activation and do not evidence adequate written description and enablement with respect to assessing measurement of a level of TRP8 activation at the time of the priority document.

5. As a result of Applicant's amendment, all rejections not reiterated herein have been withdrawn by the examiner.

6. Claims 17 and 24-36 are pending.

Election/Restriction

7. Applicant's election with traverse of Group IV, to the extent of human TRP8 of SEQ ID NO:4, claim 17 in Paper No. 14 submitted 3-24-03, is acknowledged. The traversal is on the ground(s) that the claimed processes of Groups I-X are not independent and distinct as required by 35 USC 121. This is not found persuasive because as set forth in the restriction requirement of 2-25-03 the products and methods are distinct as claimed and directed to divergent compounds, steps, effects and outcomes. A search for any one product or method is not co-extensive with any other and search and examination of the multiple groups in a single application bears undue burden upon the Examiner.

The requirement is still deemed proper and is therefore made FINAL

8. Claims 17 and 24-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

Instant amendment of 4-7-05 clarifies the invention in terms of the specification effective to receive the benefit of the noted priority date of 4-17-00 and removes Zucker

as noted prior art. Applicants assert that guidance is provided to suitable assays as denoted within the specification, for assessing TRP8 activation as indicated via Hoffman, Liu and Parawitt with respect to TRPM5 (published in 2003) and for electrophysiological monitoring as in Gillo, Burnashev and Hu (published within 1994-1996). However, Hoffman Liu and Parawitt were not privy to the artisan and the time of invention in 2000, (i.e., the references were published in 2003). While Gillo, Burnashev and Hu evidence methods for assessing electrophysiological measurement including of calcium flux, the references are not on point to TRP8 and do not clarify such measurements with respect to TRP8 activation. The artisan must be able to determine for any of the claims whether those response measured correspond to one of activation in comparison to the control. Clearly each measurement may yield opposite results indicating in contrast to activation, inhibition or represeion. Without guidance to delineate which measurements constitute "activation" from some other response, the artisan is unable to make and use the invention so as to assess compounds that induce a bitter taste.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed sequences without further undue experimentation.

9. Claims 17 and 24-36 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification describes a polypeptide sequence consisting of SEQ ID NO:r, which is shown to exhibit increased calcium flux into the cell when in contact with a compound that induces the perception of a bitter taste. The claims recite measuring levels of TRP8 activation, yet the claims do not constitute any relationship for calcium or any other molecule which is indicated as one of activation. The measurements instead encompass all responses utilizing any of the different modes of measurement yet none is correlated to TRP8 activation or perception of a bitter taste. The instantly disclosed, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera directed at any means for assessing TRP8 activation without disclosure of what measurements indicate activation. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is

claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Here only a single association is disclosed and the claims do not specifically delineate it.

Instant amendment of 4-7-05 clarifies the invention in terms of the specification effective to receive the benefit of the noted priority date of 4-17-00 and removes Zucker as noted prior art. Applicants assert that guidance is provided to suitable assays as denoted within the specification, for assessing TRP8 activation as indicated via Hoffman, Liu and Parawitt with respect to TRPM5 (published in 2003) and for electrophysiological monitoring as in Gillo, Burnashev and Hu (published within 1994-1996). However, Hoffman Liu and Parawitt were not privy to the artisan and the time of invention in 2000, (i.e., the references were published in 2003). While Gillo, Burnashev

and Hu evidence methods for assessing electrophysiological measurement including of calcium flux, the references are not on point to TRP8 and do not clarify those measurements that constitute TRP8 activation. Accordingly, adequate written description is not provided.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 17 and 24-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 is directed to a method for identifying a compound that induces the perception of a bitter taste comprising "measuring the level of TRP8 activation." Yet the artisan cannot discern the metes and bounds of "TRP8 activation." While the specification sets forth that calcium influx upon ligand binding is associated with the perception of a bitter taste, such limitations cannot be read into the claims from the specification. Moreover, while dependent claims 24-36 provide for various methods of "measuring the level of TRP8 activation" the claims do not delineate those measurements that are of "activation" vs., for example a neutral response or inhibition. For example, while the art tends to support increased calcium influx, see below, the claims are not so limited. Just measuring calcium for example would not clarify that the levels measured were of increased flux and hence of activation. Accordingly the claims are in part incomplete to those measurements constituting activation. Thus, the metes

and bounds of the claim recitations remain indefinite to one of skill in the art because the claims do not delineate those measuring responses which are deemed to be "activating" responses.

As previously argued by Applicants "an increase in the activation of TRP8 results in an influx of calcium into the taste cell and a corresponding neural stimulation of bitter taste. Alternatively, the ability of a compound to inhibit bitter tastant induced calcium influx results in inhibition of signal transduction mediated by TRP8. See Specification, generally, at 5.5 "Screening Assays for Drugs and Other Chemical Compounds Useful in Regulation of Taste Perception", pages 15- 23.

Further support for the functional limitations of the presently claimed method for activation of TRP8 protein or nucleotide is described in the Specification as "the ability of a test molecules to modulate the activity of TRP8 may be measured using standard biochemical and physiological techniques...," see Specification at page 17, lines 12- 13. Also, the activation of the "cells expressing the TRP8 channel protein are exposed to a test compound or to vehicle controls (e.g. placebos)...the cells can be assayed to measure the expression and/or activity of components of the signal transduction pathway of TRP8, or the activity of the signal transduction pathway itself can be assayed", see Specification at page 17, lines 7-11.

The courts hold that "patents are written by and for skilled artisans" otherwise it would require every patent document to include a technical treatise for the unskilled reader. This requirement has been long rejected of patent disclosures. See S3 *Inc. v NVIDIA Corp.,* 259 F.3d 1364, 1371 (Fed. Ck. 2001) citing *Atmel Com. v Information Storage Devices, Inc.,* 198 F.3d 1374 at 1382. The law is clear that patent documents need not include subject matter that is known in the field of the invention and is in the prior art. See *Vivid Technologies, Inc. v American Science and Engineering, Inc.,* 200 F.3d 795, 804 53 USPQZd 1289, 1295 (Fed. Cir. 1999).

These arguments have been fully considered but are not persuasive. Applicant's position is that the artisan would know how to measure "TRP8 activation" and that no further clarification need be provided. To the extent that the specification and prior art teach that calcium influx is a noted effect mediating bitter taste, (see also original rejection), the skilled artisan could at least surmise upon reading the specification that calcium ion influx would be considered an activator and that inhibition of this response would be considered an inhibitor. However, this is only upon reading the specification into the claims which is not permitted. Applicant's have not pointed to any definition within the specification or prior art references that directs the artisan to those measurements constituting "activation of TRP8." The rejection of record notes that no definitive activity or means of measurement is specified by the specification or claims and no standard of such measurement is recognized in the prior art. The specification notes many standard biochemical and physiological techniques. For example p. 22-23 paragraph spanning teaches that :

"The ability of a test molecule to modulate the activity of TRP8 may be measured using standard biochemical and physiological techniques. Responses such as activation or suppression of catalytic activity, phosphorylation or dephosphorylation of TRP8 and/or other proteins, activation or modulation of second messenger production, including changes in cellular ion levels, association, dissociation or translocation of signaling molecules, or transcription or translation of specific genes may be monitored. In non-limiting embodiments of the invention, changes in intracellular Ca2+ levels may be monitored by the fluorescence of indicator dyes such as indo, fura, etc. In addition activation of cyclic nucleotide phosphodiesterase, adenylate cyclase, phospholipases ATpases and Ca2+ sensitive release of neurotransmitters may be measured to identify compounds that modulate TRP8 signal transduction. Further, changes in membrane potential resulting from modulation of the TRP8 channel protein can be measured using a voltage clamp or patch recording methods."

Hence, it is clear that the specification and claims are intended to encompass more, i.e., other assays indicative of activation or inhibition. However, the specifics of such other measurements and direction as to which ones are deemed activators vs. inhibitors is not provided by the specification or prior art. Moreover, this passage is directed to "modulation" of activity of TRP8. The activity may be one of activation or conversely inhibition, especially in light of Applicants amendment to the claims as newly directed to induction and inhibition of the perception of a bitter taste and either an increase, decrease or neutral response. What is missing is a description of those effects that constitute activation (other than Ca++ influx) vs. some other modulation of activity of TRP8 (i.e., inhibition). For example, would phosphorylation measurements of a particular protein constitute activation or inhibition? Dephosphorylation? While the specification does note that an increase in the activation of TRP8 results in an influx of calcium into the taste cell and that such is deemed to be indicative of a bitter taste, the claims are not so directed or limited to calcium influx and the specification is clear that other measurements are encompassed. Yet the specification, claims and prior art fail to teach which measurements other than calcium influx are indicative of 'activation' and the claims are not so limited. The specification is further clear that some of the responses activate while others inhibit. Thus, the claims cannot be considered only broad, but instead are indefinite because those activities which constitute activation vs.inhibition of TRP8 are not distinguishable or separately noted, and because no recognized means of ascertaining these differences is provided. Further the prior art does not apparently establish these specifics, particularly in light that TRP8 is not noted

to share all functions with its other family members, see Estacion et al., and Okada et al., previously of record. The scope of the claim remains indefinite and incomplete, even to the skilled artisan.

The Examiner suggests that importation of the limitations of claim 24 into claim 17 and clarification that the measurement that indicates "activation" of TRP8 is a measurement of increased levels of intracellular Ca2+ in the cell, (in comparison as claimed) may expedite prosecution.

Status of Claims

12. No claims are allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

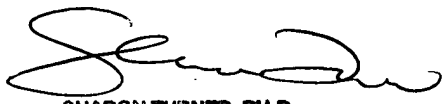
14. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.

Sharon L. Turner, Ph.D.
June 22, 2005



SHARON TURNER, PH.D.
PRIMARY EXAMINER

6-22-05